AD_____

Award Number: W81XWH-08-2-0125

TITLE: Neural and Behavioral Sequelae of Blast-Related Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Harvey S. Levin, Ph.D.

CONTRACTING ORGANIZATION: Baylor College of Medicine
Houston, TX 77030

REPORT DATE: September 2012

TYPE OF REPORT: Revised Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2012	Revised Final	1 September 2008 – 31 August 2012

4. TITLE AND SUBTITLE

Neural and Behavioral Sequelae of Blast-Related Traumatic Brain Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0125

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Harvey S. Levin, Ph.D.

E-Mail: hlevin@bcm.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Baylor College of Medicine
Houston, TX 77030

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Traumatic brain injuries (TBI) are a common occurrence from roadside blasts of improvised explosive devices (IEDs). In the proposed cross-sectional study, we aim to apply neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related MTBI. We will accomplish this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients who have experienced blast injuries, 15 civilian MTBI patients with mechanical closed head injuries, 15 military and 15 civilian patients with orthopedic injuries. Year one of the project has been devoted to the development of the necessary infrastructure for the execution of this complex multisite study. A number of development tasks have been undertaken, including hiring and training a new coordinator in Houston, developing uniform procedures for analysis of image data in Cleveland and Houston, and further developing the avenues for recruitment of subjects. Years two and three were devoted to the recruitment of subjects. We have recruited 63 subjects and acquired cognitive data from 62 and imaging data from 57 of these subjects. We completed recruitment of subjects, scoring and entering of outcome data, and continue imaging data analysis.

15. SUBJECT TERMS
Blast-related traumatic brain injury (TBI), fMRI, DTI, cognition

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	53	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION

Traumatic brain injury (TBI) is a common occurrence from roadside blasts of improvised explosive devices (IEDs). Like civilian TBI, blast-related TBI can result from mechanical forces in which objects in motion strike the head or the head is forcefully put into motion and strikes an object. TBI from exposure to an explosive blast may also result from a third cause: barotrauma. Blasts produce wave-induced changes in atmospheric pressure, which in turn produce characteristic injuries to vulnerable bodily regions at air-fluid interfaces, such as the middle ear. It is unknown whether the neural and cognitive sequelae of blast-related TBI differ from those resulting from mechanically-induced TBI commonly observed in civilian accidents. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions.

In this cross-sectional study, we applied neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related MTBI. This was accomplished by comparing neurobehavioral and neuroimaging findings obtained from military personnel who had a blast injury with those obtained from civilians who sustained TBI from motor vehicle accidents and from military and civilian control participants with orthopedic injuries. We accomplished this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients with blast injuries, 15 civilian MTBI patients with mechanical closed head injuries,15 military and 15 civilian patients with orthopedic injuries.

BODY

The final year of the project was devoted to completion of the data acquisition and the establishment of a new imaging data collection site at the Michael E. De Bakey Veterans Affairs Medical Center (MEDVAMC). A number of development tasks were then undertaken to develop cross-platform analyses to provide reliable methods for completing the image analyses. While some problems were encountered during the study, each of these was successfully managed to the exacting standards of the Principal Investigators. This meticulous work laid the groundwork for high integrity in the collection and analysis of the data. Details regarding each of these tasks are provided below, broken down by category.

Staff Recruitment, Employment, Organization, Training. There were no changes in staff in Houston. All study team members have completed all necessary Baylor and VA annual training.

Neuropsychological and Neurobehavioral Measures
All screening and outcome data have been collected; forms have been scored and entered into an Access database. All electronic files have been backed up on a local drive.

MRI

- Brain Imaging Protocols: Combining brain imaging data across multiple research sites was a considerable technical challenge. Extensive work was done to establish a good matching of the scan parameters and to confirm the acquisition of comparable, high quality images for the Cleveland Clinic, Houston HNL, and the MEDVAMC scanners (all are Siemens 3T Trio MRI scanners).

- The imaging contract with the Human Neuroimaging Laboratory (HNL) at Baylor College of Medicine expired in December 2010 and the Houston site's fMRI data acquisition was completed at the MEDVAMC.

- fMRI, DTI, and MRI Volumetric Data Acquisition: On 4/26/2011 Dr. Erik Beall, a project physicist at the Cleveland Clinic, visited the Houston site and during that trip he met with the local examiners and reviewed data acquisition procedures, he examined the MEDVAMC's scanner and other data acquisition hardware, he

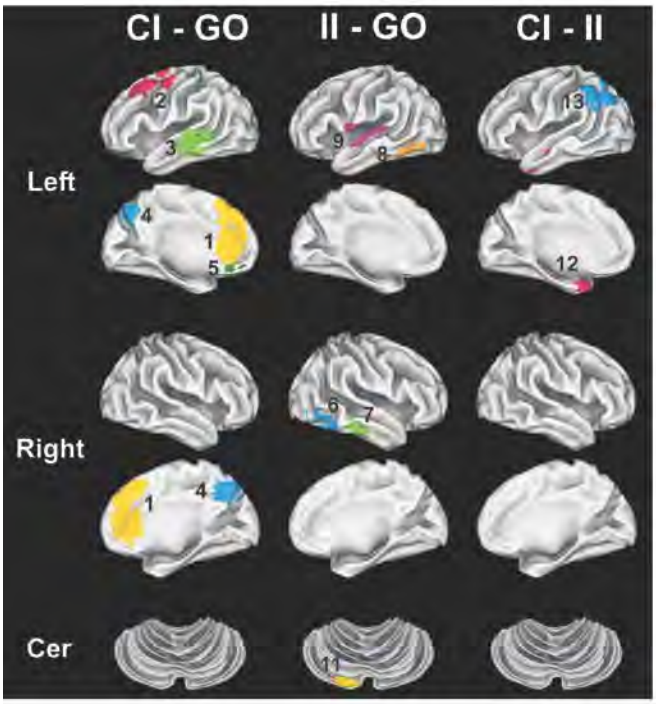
set up and tuned pulse sequences, and he obtained MRI test data for quality assessment using a normal volunteer subject. Data obtained during the testing were generally of good quality and the MEDVAMC scanner was then used to complete all remaining imaging at the Houston site. During the study the Houston MEDVAMC imaged 14 military TBI subjects, 15 military orthopedic injury and uninjured control subjects, 14 civilian TBI subjects, and 14 civilian orthopedic injury control subjects. All image data have been transferred and are archived at the image analysis laboratories in both Houston and Cleveland.

- fMRI Data Analysis: As seen in Figure 1, analyses for the Stop Signal task were performed at the Cleveland site using subtraction of activation associated with GO trials (when the participant responded to a "Go" signal) from correct inhibition (CI) activation (stopping a "Go" response in time when the stop signal came on), activation on GO trials subtracted from incorrect inhibition (II) trials (failing to stop a response in time), and activation on II trials subtracted from CI trials. This analysis disclosed a distinct pattern of brain activation in the military TBI group who exhibited increased activation associated with incorrect inhibition (II in Figure 1) on stop trials. For comparison, the civilian TBI group showed hypoactivation on incorrect inhibition trials, suggesting that blast TBI might be associated with a distinct pattern of brain activation on this task. Pending replication, we suggest that fMRI using the Stop Signal task might provide a biomarker for mild blast TBI. The Cleveland and Houston groups have collaborated on a manuscript which is under review.

- Datasets from the Sternberg Item Recognition Task (SIRT) from 52 subjects at the Houston site and 58 subjects at the Cleveland site have been processed. Currently we are performing additional analyses with the SIRT data, including analyses taking PCL-C scores into account.

- DTI, Volumetric MRI Data Analysis: We are up to date in the analysis of MRI volumetric data of brain regions. In addition we are communicating with the Cleveland group concerning analysis of the DTI data.

- Houston Recruitment: We have recruited 17 military TBI subjects (all male), 15 military controls with orthopedic injuries and uninjured subjects (11 male/4 female), 16 civilian TBI (9 male/7 female), and 15 civilian orthopedic injuries d (9 male/6 female) subjects



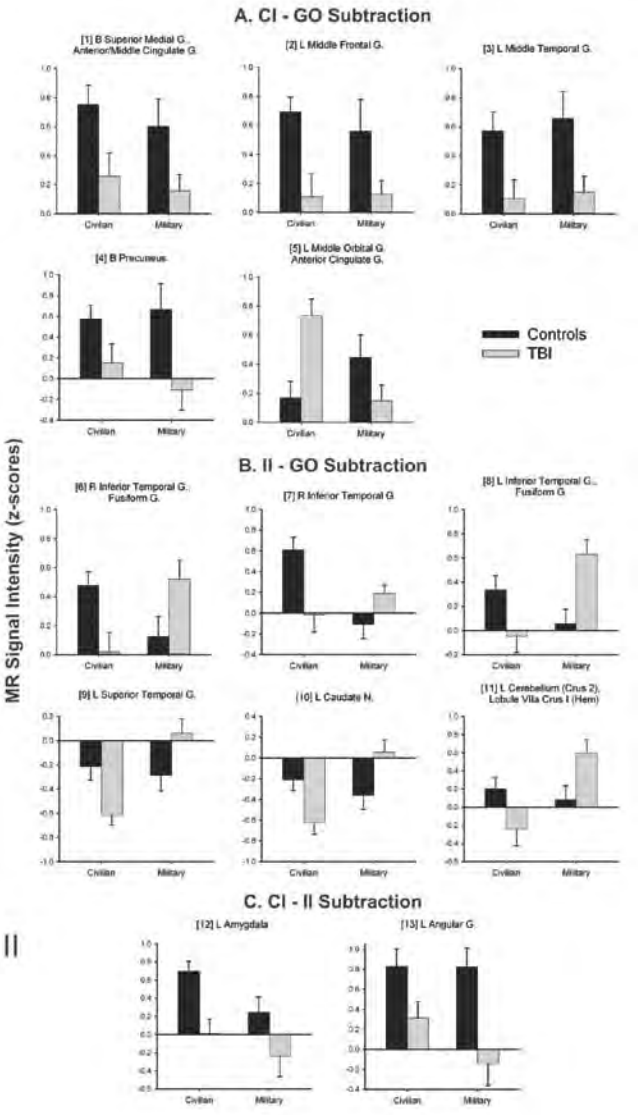


Figure 1. Functional ROIs (shown in color in upper panel) demonstrating significant main or interaction effects for the CI– GO, II – GO, and CI - II subtractions. Numbers correspond with brain region described in panel on right, which presents bar graphs illustrating significant main and interaction effects for the CI– GO, II – GO, and CI - II subtractions. CI = correct inhibition, II = incorrect inhibition, GO =go conditions. Note that regions 1-5 are from the CI – GO subtraction, regions 6-11 from the II – GO subtraction, and regions 1213 are from the CI-II subtraction. Error bars =s.e.m.

KEY RESEARCH ACCOMPLISHMENTS

The key accomplishments at the completion of the project in Houston can be summarized as:

- Chronic effects of blast related mild traumatic brain injury (mTBI) in Veterans include reorganization of the brain's functional architecture for inhibitory control as reflected by a pattern of activation on the stop signal task which differs from control groups without mTBI.
- In comparison with civilians who sustained mTBI by non-blast mechanisms such as motor vehicle crashes and sports, Veterans with chronic blast TBI exhibit increased brain activation on trials when they failed to make a correct inhibitory response.
- Functional magnetic resonance imaging findings during the stop signal task indicate a distinct pattern of brain activation which may have diagnostic implications pending replication.
- The relation of working memory-related brain activation to memory load on the Sternberg Item Recognition Task differs in Veterans with chronic blast related mTBI as compared with civilian mTBI and control groups without mTBI. Modulation of activation by increasing the memory load is altered in the caudate and cerebellum of Veterans with chronic blast related mTBI as compared with civilian mTBI. Pending further analysis of our data and replication, these findings on the Sternberg indicate distinct effects of blast related mTBI on the neural network supporting working memory in Veterans. The data are being further reviewed and a manuscript is in preparation.

REPORTABLE OUTCOMES

The Houston and Cleveland groups have collaborated on submission of a manuscript reporting the results for the Stop Signal task. We anticipate collaboration on additional papers, including the Sternberg Task and possibly the DTI data.

In April, 2013 Dr. Levin and Dr. Rao submitted pre-application #130547 to CDMRP entitled "Violent Criminal Offenses by Veterans in Relation to Traumatic Brain Injury Sustained During Deployment: Brain Imaging, Behavior, and Genetics**"** The pre-application proposes to use the Stop Signal task, directly building on accomplishments of this CDMRP grant.

Presentations:
*Deborah Warden Lectureship: Neurobehavioral Outcome of Blast Related Traumatic Brain Injury: Current findings, Implications for Clinical Services and Directions for Research***.** 5th Annual Defense and Veterans Traumatic Brain Injury Summit, National Harbor, MD, 2011

Chronic Outcome of TBI in Blast Brain Injury Subjects. National Neurotrauma Society Annual Meeting 2012, Phoenix, AZ

Diffusion Tensor Imaging: Co-morbidities, Complications, and Controversies. 8th Annual Blast Injury Conference, Organized by Polytrauma Program, Veterans Affairs Medical Center, December 14, 2011 Tampa, FL

CONCLUSION

Blast related mTBI in Veterans appears to be associated with a distinctive pattern of brain activation on the Stop Signal Task, a measure of response inhibition. This pattern, which differs from Veterans who did not sustain TBI during deployment and from civilians who sustain non-blast mTBI, may have clinical application pending replication.

REFERENCES

A manuscript on the Stop Signal fMRI task (summarized above) has been submitted to the *Journal of Neurotrauma* and is currently under editorial review at the time of this writing.

APPENDICES

Manuscript submitted to *Journal of Neurotrauma* is appended to the end of this report.

SUPPORTING DATA

None at this time

Journal of Neurotrauma

Journal of Neurotrauma: http://mc.manuscriptcentral.com/neurotrauma

Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury

Journal:	*Journal of Neurotrauma*
Manuscript ID:	NEU-2013-2877.R1
Manuscript Type:	Regular Manuscript
Date Submitted by the Author:	n/a
Keywords:	MRI, TRAUMATIC BRAIN INJURY, BIOMARKERS, NEUROPSYCHOLOGY, OTHER TOOLS OF MODERN IMAGING

Complete List of Authors:
Fischer, Barbara; Wm. S. Middleton VA Hospital, GRECC
Parsons, Michael; Cleveland Clinic Foundation, Neuropsychology
Durgerian, Sally; Medical College of Wisconsin, Neurology
Reece, Christine; Cleveland Clinic Foundation, Center for Brain Health
Mourany, Lyla; Cleveland Clinic Foundation, Center for Brain Health
Lowe, Mark; Cleveland Clinic Foundation, Diagnostic Radiology
Beall, Erik; Cleveland Clinic Foundation, Imaging Institute
Koenig, Katherine; Cleveland Clinic Foundation, Diagnostic Radiology
Jones, Stephen; Cleveland Clinic, Diagnostic Radiology
Newsome, Mary; Baylor College of Medicine, PM&R Cognitive Neuroscience Laboratory; Michael E DeBakey VA Medical Center, Research TBI Center of Excellence
Scheibel, Randall; Baylor College of Medicine, Physical Medicine & Rehabilitation
Wilde, Elisabeth; Baylor College of Medicine, Physical Medicine and Rehabilitation; Baylor College of Medicine, Radiology
Troyanskaya, Maya; Baylor College of Medicine, Physical Medicine & Rehabilitation
Merkley, Tricia; Baylor College of Medicine & the University of Texas-Houston Medical School, Physical Medicine and Rehabilitation Alliance
Walker, Mark; Case Western Reserve University, Neurology; Cleveland Veterans Affairs Medical Center, Neurology
Levin, Harvey; Baylor College of Medicine, Cognitive Neuroscience Laboratory
Rao, Stephen; Cleveland Clinic, Schey Center for Cognitive Neuroimaging;

Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury

Barbara L. Fischer,[1] Michael Parsons,[2] Sally Durgerian,[3] Christine Reece,[2]

Lyla Mourany,[2] Mark J. Lowe,[4] Erik B. Beall,[4] Katherine A. Koenig,[4]

Stephen E. Jones,[4] Mary R. Newsome,[5,6] Randall S. Scheibel,[5,6]

Elisabeth A. Wilde,[5,6] Maya Troyanskaya,[5,6] Tricia L. Merkley,[5,6] Mark Walker,[7,8]

Harvey S. Levin,[5,6] and Stephen M. Rao[2,*]

[1] Geriatric Research Education and Clinical Center (GRECC), Wm. S. Middleton Memorial Veterans Affairs Hospital, Madison, Wisconsin

[2] Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA

[3] Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[4] Imaging Institute, Cleveland Clinic, Cleveland, Ohio, USA

[5] Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA

[6] Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas

[7] Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio, USA

[8] Department of Neurology, Case Western Reserve University, Cleveland, Ohio, USA

*Address correspondence to:

Stephen M. Rao, PhD
Schey Center for Cognitive Neuroimaging
Neurological Institute
Cleveland Clinic
9500 Euclid Avenue / U10
Cleveland, OH 44195
216-444-1025 (voice)
216-445-7013 (fax)
Email: raos2@ccf.org

Abstract

Military personnel involved in Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) commonly experience blast induced mild to moderate traumatic brain injury (TBI). In this study, we used task-activated functional MRI (fMRI) to determine if blast-related TBI has a differential impact on brain activation in comparison to TBI caused primarily by mechanical forces in civilian settings. Four groups participated: (1) blast-related military TBI (milTBI; n=21); (2) military controls (milCON; n=22); (3) non-blast civilian TBI (civTBI; n=21); and (4) civilian controls (civCON; n=23) with orthopedic injuries. Mild to moderate TBI (MTBI) occurred 1 to 6 years prior to enrollment. Participants completed the Stop Signal Task (SST), a measure of inhibitory control, while undergoing fMRI. Brain activation was evaluated with 2 [mil, civ] X 2 [TBI, CON] ANOVAs, corrected for multiple comparisons. During correct inhibitions, fMRI activation was lower in the TBI than CON subjects in regions commonly associated with inhibitory control and the default mode network. In contrast, inhibitory failures showed significant interaction effects in the bilateral inferior temporal, left superior temporal, caudate, and cerebellar regions. Specifically, the milTBI group demonstrated more activation than the milCON group when failing to inhibit; in contrast, the civTBI group exhibited less activation than the civCON group. Covariance analyses controlling for the effects of education and self-reported psychological symptoms did not alter the brain activation findings. These results indicate that the chronic effects of TBI are associated with abnormal brain activation during successful response inhibition. During failed inhibition, the pattern of activation distinguished military from civilian TBI, suggesting that blast-related TBI has a unique effect on brain function that can be distinguished from TBI resulting from mechanical forces associated with sports or motor vehicle accidents. The implications of these findings for diagnosis and treatment of TBI are discussed.

Keywords: Traumatic brain injury, fMRI, brain activation, inhibitory control, blast-related TBI, mechanical TBI

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Introduction

Traumatic brain injury (TBI) is common in military personnel involved in the Operations Iraqi Freedom and Enduring Freedom (OIF/OEF) conflicts.[1-4] Epidemiological studies suggest that the prevalence of TBI ranges from 15-28%[1, 5, 6] with a majority of these TBIs (50-79%) resulting from blasts caused by improvised explosive devices.[1, 7, 8]

Blast induced TBI may involve different mechanisms than TBI occurring in civilian settings. Whereas most head trauma in civilians results from mechanical processes such as acceleration/deceleration or rotational forces[9], blast induced TBI is thought to result from rapid changes in atmospheric pressure producing over- and/or under-pressurization. Blast-related damage is thought to occur within internal organs, particularly at air-fluid junctures.[10] Hypothesized mechanisms of blast induced brain injury include transcranial or intravascular propagation of blast energy, as well as indirect transmission via cerebrospinal fluid through the foramen magnum.[2] In addition to injury caused by these primary blast forces, damage may result from mechanical forces resulting from displaced projectiles such as bricks, nails, etc. (secondary blast forces). A third form of blast injury occurs following the structural disintegration of buildings and vehicles leading to crush injuries or of individuals being slammed into hard surfaces (tertiary blast forces). Thus, military personnel frequently experience both the pressurization effects of blast in combination with mechanical forces (blast + mechanical), and may sustain multiple such injuries over the course of their deployment.[11]

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Animal models have revealed numerous pathological, biochemical and behavioral changes as a result of blast exposure.[3] Among the blast sequellae noted in animals are diffuse axonal injury[12], sub-arachnoid and parenchymal bleeding[13], increases in intracranial pressure [14], evidence of hippocampal neurodegeneration, phosphorylated tau protein and astrocytosis[15], vasospasm and white matter degeneration[16], increased levels of mortality, brain edema[17], and downregulation of genes associated with hippocampal neurogenesis.[18] Despite these advances in knowledge from animal models, there remains controversy as to whether the clinical and neuropathological features of blast and mechanical TBI are the result of a unitary mechanism of injury[15] or the result of unique and distinguishable injury parameters.[16, 17]

Attempts to distinguish blast-related from mechanical TBI in humans have met with mixed results. Mild to moderate TBI's typically do not have macroscopic abnormalities on structural MRI. Although we have observed subtle differences in cognitive performance in blast-related TBI[19], the cognitive deficits observed in the acute and subacute stage of mild to moderate TBI typically resolve in the chronic stage. Belanger et al.[20] have suggested that any differences between blast-related and mechanical TBI are likely the result of increased levels of psychological distress in blast-related TBI rather than any unique differences in brain pathology. An alternative strategy for differentiating blast-related from mechanical TBI is to identify unique neural signatures in brain activation patterns using fMRI. Several fMRI studies have identified anomalous brain activation patterns in mechanical[21, 22] and blast-related[23] TBI compared to non-TBI control groups, but none to date has directly compared blast-related and mechanical TBI.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

In this task-activated fMRI study, we compared blast-related and mechanical TBI using a measure of response inhibition, the Stop Signal Task (SST). Response inhibition involves the ability to stop or suspend an intended or initiated action.[24] Problems with inhibitory control are common in mild to moderate TBI.[25, 26] To our knowledge, only one fMRI study has evaluated inhibitory control in blast-related TBI. Matthews et al.[27] compared OEF/OIF Veterans who had experienced blast-related concussion with either loss of consciousness (LOC) or alteration of consciousness (AOC) using the SST. While the two groups did not differ in task performance, TBI individuals with LOC demonstrated significantly reduced activation in the left ventromedial prefrontal cortex than those with AOC on "easy" trials. There were no significant group differences in activation on "difficult" trials. The study did not compare blast-related TBI to civilian TBI nor to healthy controls.

The present fMRI study, therefore, was designed to identify possible differences between blast-related and mechanical TBI in the brain activation patterns evoked by an inhibitory control task (SST). Our focus was on the long term neural sequelae, with our TBI participants at least 12 months post injury. In addition to the military blast-related TBI and civilian non-blast TBI participant groups, we recruited two healthy control groups: a military group with combat exposure during the OEF/OIF conflict and a civilian group who experienced an orthopedic injury. We hypothesized that brain activation patterns would discriminate TBI and healthy control groups and, most importantly for this study, blast-related and mechanical TBI groups.

Materials and Methods

Participants. All procedures and recruitment strategies were reviewed and

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

approved by the institutional review boards of the Cleveland Clinic, Stokes Veterans Affairs Medical Center-Cleveland (VAMC), and the U.S. Department of Defense; participants provided written informed consent. Four groups of participants were enrolled: (1) OEF/OIF Veterans with blast-related MTBI (*milTBI*), (2) deployed OEF/OIF Veterans, who never experienced blast and/or head injury, served as milTBI controls (*milCON*), (3) civilians with MTBI (*civTBI*) due to sports or motor vehicle accidents, and (4) civilians with orthopedic injuries served as civTBI controls (*civCON*).

Veterans were recruited primarily through letters mailed out from the Cleveland VAMC. The pool for recruitment included all OEF/OIF Veterans who had registered for VAMC-related services (not restricted to head injury). Letters were sent to those individuals describing the study and inviting them to participate if they suffered a head injury (milTBI) or served but did not suffer a head injury (milCON). Veterans were also recruited via referral to the study from a VAMC physician and through advertisements posted at local colleges and in newspapers. Civilian participants were recruited primarily through informational mailings sent from their treating physician at the Cleveland Clinic.

Potential participants initially underwent telephone screening to determine eligibility. Those participants meeting inclusion/exclusion criteria (see below) were invited to undergo a neuroimaging examination at the Cleveland Clinic. Attempts were made to match the four groups with regard to age, gender, education, and, in the case of TBI participants, time since injury. Specific details of the inclusion/exclusion criteria for each group are as follows:

milTBI participants sustained a blast-related TBI during deployment between 1

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

and 6 years prior to enrollment. In order to be considered eligible for inclusion, prospective participants must have experienced a blast induced injury that resulted in LOC, AOC, or a period of post-traumatic amnesia (PTA), following the event. This was assessed via self-report, but with trained interviewers who probed/clarified responses in an attempt to obtain the most accurate information possible (e.g., distinguishing true AOC from "fog of war"). If there was a LOC, it must not have exceeded 24 hours in duration and, if PTA occurred, it must not have exceeded 7 days. Furthermore, milTBI participants had no observable intracranial injury on computer tomography (CT) scan (if available) and their Glasgow Coma Scale (GCS) score was between 9 and 15 (if available). For those participants with multiple head injuries, the most severe served as the "index injury" for purposes of estimating time since injury.

milCON served in active OEF/OIF duty within the prior 6 years but had no history of brain injury, primary blast exposure, or LOC during their deployment. This group controlled for the nonspecific emotional distress associated with combat. These participants had no history of TBI either pre- or post-deployment.

civTBI participants sustained a mild to moderate TBI through common non-blast mechanisms, such as motor vehicle accident or sports-related injuries. The head injury must have occurred 1-6 years prior to enrollment. Duration of LOC and PTA, derived from medical records and self-report, must not have exceeded 24 hours and 7 days, respectively. Participants were excluded if there was an observable intracranial injury on brain imaging (if available). GCS score was between 9 and 15 (if available). As with milTBI participants with multiple head injuries, the most severe served as the "index injury" for estimating time since injury.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

civCON were chosen to control for nonspecific effects of injury on cognitive and brain imaging data. These participants had no history of brain injury or LOC, and no primary blast exposure. Extra-cranial injuries were experienced during the prior 6 years and included ligament damage and fractures of the arms and legs due to sports or motor vehicle accidents.

All prospective participants were excluded if any of the following were present: not fluent in English, history of neurologic disorders associated with cerebral dysfunction and/or cognitive deficit (e.g., cerebral palsy, mental retardation, epilepsy), history of severe psychiatric disorder (e.g., bipolar disorder, schizophrenia) with the exception of post-traumatic stress disorder (PTSD), penetrating gunshot wound to the brain or contraindications to undergoing MRI (e.g., pregnancy, metal implants, claustrophobia). Potential participants were also excluded based on: (1) significant alcohol and/or drug abuse by administration of the Alcohol Use Disorders Identification Test (AUDIT)[28] (cutoff score < 20) and the Drug Abuse Screening Test-10 (DAST-10)[29] (cutoff score < 4); (2) pre-injury psychiatric history based on responses to the Structured Clinical Interview for the DSM-IV Axis-I Disorders (SCID; Overview Module of the Non-Patient Research version November, 2002[30]; and (3) symptom invalidity using a combination of Green's Word Memory Test (WMT)[31] and performance on the neuropsychological test battery.

Self-report measures. The Neurobehavioral Symptom Inventory (NSI)[32] was administered to characterize commonly self-reported symptoms associated with concussion. Severity of PTSD symptoms over the past month was measured with the PTSD Checklist – Civilian version (PCLC)[33]. Self-reported depression symptoms were

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

assessed with the Center for the Epidemiological Study of Depression Scale (CES-D).[34] Self report of pain and fatigue were measured using visual analog scales ranging from 0 - 10.

Neuropsychological measures. Participants completed a standard battery of neuropsychological tests designed to measure cognitive deficits most commonly associated with mild TBI. The battery included measures of information processing speed, executive function, and memory: written and oral forms of the Symbol Digit Modalities Test (SDMT)[35], parts A and B of the Trail Making Test (TMT)[36], Controlled Oral Word Association Test (COWAT)[37], and the California Verbal Learning Test-2 (CVLT-2).[38]

Stop Signal Task (SST). The SST paradigm used in this study was similar to that described by Aron and Poldrack[39] and illustrated in Figure 1. The SST consisted of 96 GO (75%) and 32 STOP (25%) trials distributed over 2 imaging runs. On all trials, the participant was presented with a 500 ms warning stimulus consisting of a central fixation cross. This was followed by a left or right arrow. For the GO trials, the participant responded as fast as possible with a left or right key press using the index and middle fingers of the right hand. For the STOP trials, a red filled box was presented above the GO (arrow) stimulus. The participant was instructed to attempt to stop his/her response at the appearance of the red box. The time between the GO (arrows) and STOP (red box) stimuli is referred to as the stop signal duration (SSD). The number of left and right arrows was equal; GO and STOP trials and left/right arrows were presented in a pseudorandom order.

The SSD on STOP trials changed depending on the participant's behavior. If the

participant inhibited successfully on a STOP trial, then inhibition was made more difficult on a subsequent STOP trial by increasing the SSD by 50 ms; if the participant did not successfully inhibit, then inhibition was made easier by decreasing the SSD by 50 ms. A single staircase was used to ensure sufficient number of both correct and incorrect inhibitions by the end of the task. Average SSD was computed, for each subject, from the values for the last 48 moves of the staircase. The stop signal reaction time (SSRT) was calculated by subtracting the average SSD from the mean of median RT on GO trials. Higher SSRT values are indicative of poorer inhibition.

The task was programmed using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA) and displayed in the scanner using an Avotec back-projection video system (Avotec, Inc., Stuart, FL).

MR Image Acquisition. Scanning was conducted at the Cleveland Clinic using a Siemens TIM Trio 3T MRI scanner (Erlangen, Germany) equipped with a 12-channel receive-only head array. Whole-brain fMRI scans were acquired with a gradient-echo, echoplanar (EPI) pulse sequence [31 4-mm thick contiguous axial slices, TE=29 ms; TR=2800 ms; flip angle=80°; FOV=256 X 256 mm; matrix=128 X 128; in-plane resolution=2 X 2 mm]. The SST task was performed over two imaging runs each lasting a total of 736 secs (263 volumes per imaging run). High resolution structural MRI (sMRI) scans [T1 with T1-weighted inversion recovery turboflash (MPRAGE), 120 axial slices, thickness 1-1.2mm, Field-of-view (FOV) 256 mm x 256 mm, TI/TE/TR/flip angle (FA) 900ms/1.71ms/1900ms/80, matrix 256x128, receiver bandwidth (BW) 62kH] were acquired for registration with lower resolution EPI images and to measure cortical and subcortical gray and white matter volumes.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Image Analysis (fMRI). The first 4 pre-steady-state volumes of the EPI timeseries were removed. The remaining images were timeshifted, motion corrected, and spatially filtered using a 2D 4mm full width at half maximum (FWHM) Gaussian filter in the Fourier domain. Multiple regression was performed using Analysis of Functional Neuroimaging (AFNI) software [40]. A gamma variate hemodynamic response function (HRF) model used regressors for four trial types: GO correct (GO), GO incorrect, correct inhibition (CI), and incorrect inhibition (II). GO incorrect trials were not subsequently analyzed due to their low frequency (see Results). Individual subject t-maps for GO, CI and II trial types were converted to z-maps and transformed to Talairach stereotaxic space (Talairach and Tournoux, 1988).

Three t-test subtraction maps (CI - GO, II – GO, and II – CI) were generated for each of the 4 groups (milTBI, milCON, civTBI, and civCON). A significant cluster was defined by an individual voxel probability ($p<.005$) and a minimum cluster size (0.684 ml); these joint thresholds set the whole brain false positive rate for a significant cluster equal to $p=0.05$. A disjunction mask was then created for each contrast by combining all suprathreshold voxels from any of the four group t-maps. This produced functional region of interest (fROI) maps for each of the three subtraction conditions. Large fROIs were divided along local minima in the averaged t-maps. Within each fROI and condition, z-statistics were averaged for each subject. For each fROI and subtraction condition, 2 (MIL/CIV) X 2 (TBI/CON) ANOVAs were conducted. False discovery rate (FDR) was used to correct for multiple comparisons. For those fROIs surviving the FDR correction, Tukey B post-hoc analyses were used to identify which groups demonstrated significant differences in the magnitude of the fMRI response.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Image Analysis (sMRI). All structural MRI scans were reviewed for TBI-related and incidental pathology by a board-certified neuroradiologist (S.E.J.). Quantitative regional brain volumes were obtained using the parcellation method incorporated in Freesurfer 5.1 software[41] using the Desikan atlas.[42] Results for each partcipant were visually inspected by a single rater to ensure accuracy of the cortical surface reconstruction. Manual editing, where necessary, was performed to optimize accuracy. The surface inaccuracies involving skull stripping or frank exclusion of brain parenchyma were edited either by (1) adding control points to aid FreeSurfer in the identification of white matter (since it uses the WM/GM boundary as a starting place for reconstructing the pial surface), (2) by fixing the skull strip by removing remaining dura, or (3) by adding back in the sections of brain that were inadvertently automatically removed. Output included 52 volumes including gray (cortical and subcortical) and white matter regions and total CSF. Correction for intracranial volume (ICV) was achieved by dividing the volume of interest by ICV and multiplying by 100. For each of the 52 volumes, 2 (MIL/CIV) X 2 (TBI/CON) ANOVAs were conducted. FDR was used to correct for multiple comparisons. For those volumes surviving the FDR correction, post-hoc group analyses were performed using the Tukey B statistic.

Results

Of 222 individuals who underwent telephone screening, 107 (48.2%) met screening criteria and were scheduled for study visits. Of those enrolled, 20 participants (7 milTBI, 4 milCON, 2 civTBI, and 7 civCON) were excluded from the final analysis for the following reasons: excessive motion in scanner (n=4), poor cooperation (n=3),

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

inability to understand test instructions (n=6), claustrophobia in scanner (n=2), incidental pathology discovered on MRI (n=1), discovery of medical condition on exclusion list (n=2), and technical problems with SST administration (n=2). The final sample consisted of 21 milTBI, 22 milCON, 21 civTBI, and 23 civCON participants (Table 1). There were no significant differences in age or gender between the four groups; participants were largely male. milTBI participants had significantly fewer years of education than the other groups. Time since the most severe injury was significantly longer for milTBI than civTBI participants (Table 1).

For the milTBI group, 5 participants (24% of the sample) had been exposed to a single blast event, 8 (38%) reported 2 blast exposures, and the remaining 8 (38%) reported multiple blast exposures (range 3 – 20). For the civTBI group, 6 (29%) participants had a history of a single concussion, 5 (24%) reported 2 concussions, and 8 (38%) reported multiple concussions (range 3-10; data on additional concussions was not available for 2 participants in this group). A chi-square analysis comparing the civTBI and milTBI groups on the proportion with multiple concussions was not significant.

Injury relevant data was gathered regarding the most severe TBI experienced. Twelve milTBI participants reported a loss of consciousness (LOC; 57%) typically ranging from a few seconds to a few minutes in duration (one subject reported a 2.5 hour LOC) and all subjects reported either PTA or AOC. Within the milTBI group, 18 participants (86%) were labeled as having an injury of mild severity due to LOC of < 30 mins and AOC/PTA of <24 hrs. The other 3 participants (14%) were characterized as having an injury of moderate severity due in one case to a reported LOC of 2.5 hours

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

and in 2 cases to a reported AOC/PTA ranging from 5 to 15 days. Within the milTBI group, 13 participants reported suffering additional non-TBI related injuries as a result of the blast episode (polytrauma; 62%).

For the civTBI group, MTBI was caused by participation in sports (13; 62%), motor vehicle accidents (4; 19%), bicycle accident (1; 4.5%), being struck by an object (2; 10%), and by a fall (1; 4.5%). Injury relevant data was gathered regarding the most severe TBI experienced. 8 participants (38%) acknowledged a LOC lasting 1 minute or less in duration. All participants reported PTA or AOC ranging in duration from a few seconds to one hour in 19 participants (mild severity; 90%) and up to a few weeks in 2 participants (moderate severity; 10%). Polytrauma was reported in 6 civTBI participants (29%).

Self-Report Measures. Participants in the milTBI group endorsed significantly more concussion-related symptoms (NSI), PTSD (PCLC), depression (CESD), and pain than did participants in the three remaining groups (Table 1). There were no group differences in self-reported fatigue.

Neuropsychological and SST Performance. Two-way (MIL/CIV vs TBI/CON) ANOVAs were conducted on each neuropsychological and SST index (Table 2). No differences in performance were identified for the main effect of TBI (TBI vs. CON). Relative to the civilian participants, the military sample performed more poorly on neuropsychological testing (oral and written versions of the SDMT, COWAT, and short delay of the CVLT-2). A significant interaction between TBI/CON and MIL/CIV was observed on the long delay of the CVLT-2; posthoc analyses indicated that the milTBI group performed worse than the civTBI group.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

On the SST (Table 2), no significant differences were observed on any of the indices for the main effect of TBI (TBI vs. CON) or for the interaction effect (TBI/CON vs. MIL/CIV). Significant effects were observed on the MIL vs. CIV main effect, with the military groups demonstrating poorer performance than the civilians, characterized by slower reaction times on GO trials, shorter SSD, and longer SSRT.

fMRI. The disjunction analysis identified 25 fROIs for the CI-GO subtraction, 39 for the II-GO subtraction, and 24 for the CI - II subtraction (see Supplementary Figure 1 and Supplementary Tables 1-3). None of the regions had a significant main effect of military service (MIL vs. CIV).

Six regions demonstrated a main effect of TBI (TBI vs. CON): bilateral superior medial frontal gyrus/anterior and middle cingulate gyrus [region #1; Figure 2 and Table 3], left middle frontal gyrus [#2], left middle temporal gyrus [#3], and bilateral precuneus [#4] for the CI-GO subtraction and left amygdala [#12] and left angular gyrus [#13] for the CI-II subtraction (Table 3). For all six regions, the TBI groups demonstrated lower activation than the control groups (Figure 3).

Seven regions demonstrated significant interaction effects: left middle orbital frontal/anterior cingulate gyrus [#5] for the CI-GO subtraction and the right and left inferior temporal gyrus/fusiform gyrus [#6 and #8], right inferior temporal gyrus [#7], left superior temporal gyrus [#9], left caudate [#10], and left cerebellum (Crus II) and cerebellar lobule VIIa/Crus I [#11] for the II-GO subtraction. The pattern of interaction effects (Figure 3) was fairly consistent across all seven regions: the civTBI group exhibited less activation than the civCON group; in contrast, the milTBI group demonstrated more activation than the milCON group.

In light of group differences in education, concussion symptoms (NSI), PTSD (PCLC), depression (CESD), and pain perception (Table 1), we conducted analyses of covariance (ANCOVAs) on each of the 13 significant brain regions. The ANCOVAs were performed with one covariate per analysis rather than with combinations of covariates. None of the covariates (education, NSI, PCLC, CESD, and pain perception) resulted in a significant main or interaction effect becoming non-significant.

sMRI. None of the participants had macroscopic lesions on sMRI scans. None of the 52 FreeSurfer-derived volumes demonstrated significant main or interaction effects after FDR correction.

Correlational Analyses. To identify possible relationships between functional brain activity and neurobehavioral measures, Spearman correlations were performed between the 13 significant fROIs (Table 3) and SST performance (SSD, Go Correct RT), cognitive testing (Trails A, Trails B-A, COWAT), and self-report ratings (PCLC, CESD, Pain, Fatigue and NSI). For the combined TBI groups, two correlations survived an FDR correction for multiple comparisons: left STG correlated significantly with the SDMT ($r = -0.61$, $p < 0.0001$) and PCLC ($r = 0.54$, $p = 0.0002$). These correlations indicate that greater activation in the left STG in response to Incorrect Inhibitions is associated with poorer performance on a measure of information processing speed (SDMT) and greater self-report of PTSD symptoms (PCLC). No significant correlations were observed for the combined control groups.

Discussion

Results from this fMRI study of inhibitory control processes may be summarized as follows: (1) relative to healthy controls, both blast-related and mechanical TBI

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

produce an underactivation when participants correctly inhibit a prepotent response, (2) when participants are unable to inhibit a response, blast-related and mechanical TBI demonstrate the opposite neural response, with the former group demonstrating hyperactivation and the latter hypoactivation relative to controls, (3) these results could not be explained by SST performance, neuropsychological test results, demographic variables, or self-reported symptoms, including a measure of PTSD, and (4) SST-related activity during failed inhibition in the left STG is correlated with poorer performance on a measure of information processing speed and greater PTSD-related complaints in the TBI group. These findings are the first to demonstrate a neural basis for distinguishing blast-related from mechanical TBI in humans. More broadly, our fMRI results are noteworthy for identifying a "neural signature" associated with TBI up to six years post injury in the absence of demonstrable cognitive deficits.

When participants correctly inhibit their responses on the SST (CI - GO and CI - II; Figure 3), TBI participants, regardless of etiology, demonstrate hypoactivation in bilateral medial prefrontal, bilateral precuneus, and left inferior parietal regions. These frontal and parietal regions are frequently associated with the default mode network (DMN), a neural system active during the resting state[43] and closely linked with semantic systems involved in reasoning, planning and problem solving.[44] Using an independent component analysis of the SST in healthy individuals, Zhang & Li[45] noted that activity in DMN regions (ventromedial prefrontal cortex, posterior cingulate/precuneus, and inferior parietal) correlates with inhibitory accuracy on the SST. Bonnelle et al.[29] also found differences in activation within DMN brain regions (precuneus, posterior cingulate cortex) between civilian TBI participants and healthy

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

controls during performance of the SST. Our results, therefore, suggest that TBI alters DMN activity during successful inhibitory processing.

Successful inhibition was also associated with decreased activation of the left amygdala in both TBI groups. Damage to the amygdala has been consistently linked with emotional sequelae of TBI in both military[46, 47] and civilian[48] settings. The location of the structure in the anterior temporal lobe makes it particularly vulnerable to injury.[49] The decreased amygdalar activation during inhibition in TBI participants suggests that emotional salience may play a less prominent role in inhibitory processes for these participants than for non-TBI controls. This is in contrast to studies of individuals with PTSD[50, 51], where the opposite pattern is observed (i.e., hyperactivation of the amygdala).

In contrast to successful inhibitions where both TBI groups demonstrated hypoactivation relative to controls, clear differences were observed between blast-related and mechanical TBI groups during unsuccessful inhibition (II-GO subtraction) in the left caudate nucleus and left posterior lobe of the cerebellum. As shown in Figure 3, the blast-related TBI group demonstrated hyperactivation in these regions relative to the military controls, whereas the mechanical TBI group showed hypoactivation relative to the civilian controls. It is noteworthy that the caudate demonstrates increased activity during feedback processing.[52] The posterior lobe of the cerebellum, in particular the hemispheric parts of lobule VIIA (Crus I and Crus II) and lobule VIIB, has multiple cognitive and emotional functions, with focal lesions resulting in impairments in executive functions, spatial cognition, language, and affect.[53] We speculate that blast-related TBI may heighten activation of brain regions that are associated with the

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

cognitive/emotional interpretation of negative feedback. In contrast, mechanical TBI results in a reduction in these same brain regions.

Incorrect Inhibitions elicited increased activation in the milTBI group relative to all other groups in bilateral inferior temporal and fusiform gyri. These regions are thought to be involved in the attentional modulation of visual engagement.[54, 55] Attentional modulation is crucial to responding to visual cues (e.g., stop signal) by filtering out goal irrelevant information quickly to successfully inhibit responses.[55] Our findings suggest that milTBI individuals may receive decreased input from orbital frontal regions on inhibition trials, contributing to inefficient compensatory overactivation of temporal regions in attending to stop cues. Hyperactivation in inferior temporal regions in the milTBI participants may be associated with difficulty in appropriately integrating, contextualizing, and responding to the ttop signal cue.

Individuals with blast-related TBI are more likely to express non-specific complaints of difficulties with executive functioning and affective disturbances than individuals who experience TBI in civilian life.[56] Indeed, our milTBI participants endorsed significantly more symptoms of PTSD, depression, pain, and postconcussion syndrome. Our brain activation results, however, remained significant even after controlling for self-reported symptoms. Our results do not support the view that self-reported symptoms, like PTSD, provide the most salient explanation for TBI cognitive symptoms.[1, 57, 58] Furthermore, we have demonstrated a distinction in fMRI activation patterns between blast-related and mechanical TBI that appears to be independent of the presence of PTSD.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

. Possible pathophysiological bases underlying our finding that task-activated fMRI discriminates blast-related from mechanical TBI may be related to recent results of a diffusion tensor imaging (DTI) study. Davenport et al.[59] found lower fractional anisotropy (FA) in white matter in blast-related military TBI compared to Veterans who had previously incurred mechanical TBI as civilians. Moreover, FA was more affected in persons with multiple blast-related exposures. We speculate that the greater disruption of white matter integrity in blast-related TBI produces a greater alteration in the activation of brain networks subserving response inhibition than in mechanical TBI.

It is important to note that we did not observe group differences in two brain regions that are traditionally associated with response inhibition. fMRI and lesion studies highlight the role of the preSMA and right inferior frontal cortex/insula in response inhibition.[39, 45, 60, 61] While these brain regions were activated by the SST (see Supplementary Figure 1), no significant group differences were observed in these two regions. In contrast, our finding of reduced activation among TBI participants in the default mode network during correct inhibitions may be consistent with other findings of decreased resting state default mode connectivity in individuals with TBI.[62, 63]

Individuals in both TBI groups demonstrated poorer inhibition (slower reaction times on GO trials, shorter SSD, and longer SSRT) than control participants. The clinical implications of poor performance on measures of response inhibition require further study. It is unclear whether poor performance is associated with impulsive decision making with poor judgment, increased driving accidents, aggressive and/or unlawful behavior, and substance use/abuse. In the military theater, impaired response inhibition may even be associated with decreased survival rates. Interestingly,

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

correlational analyses showed that activation in one brain region, the left STG, was associated with failed inhibition and increased PTSD symptoms in TBI patients. The precise meaning of this relationship is difficult to discern since no other relationships were observed between brain activity and neurobehavioral measures,

Relative to other fMRI studies in TBI, our sample size is large. In addition, the four group composition allowed us not only to compare TBI with controls, but also blast-related with mechanical TBI. It is also the first study to examine the inhibitory control circuits disrupted by blast-related TBI. This study is not without limitations, however. First, it is important to note that what we are calling a blast-related TBI is more likely a combination of pressurization changes associated with blast plus secondary and tertiary mechanical forces. In effect, we are comparing blast+mechanical versus mechanical TBI, since in all likelihood pure blast-related injuries occur rarely in the combat theater. Second, the SST is designed to achieve approximately 50% correct inhibitions. Although our task achieved somewhat less than 40% correct inhibitions, we had enough trials (n>12) to successfully generate brain maps for the CI condition. Third, the diagnosis of blast-related TBI is based on self-report, since military personnel who experience a mild to moderate TBI are rarely removed from the combat theater and medical records are minimally recorded. Fourth, despite our best attempts to equate the four groups based on demographic variables, the milTBI group was less educated than the two civilian groups. When education was used as a covariate, the fMRI findings remained significant. Fifth, we did not observe differences between TBI and control groups on SST performance and neuropsychological testing. The absence of a TBI effect is likely attributable to the reduced sensitivity of cognitive measures to

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

mild/moderate TBI during the chronic post-injury period. Sixth, the time since injury was significantly shorter in the mechanical (29.7 months) than blast-related (52.9 months) TBI groups. Both groups, however, were clearly in the chronic stage post-injury. Furthermore, when this variable served as a covariate, it did not influence the fMRI results. Seventh, we would have preferred to recruit milCON participants who had experienced an orthopedic injury to equate with the civCON group. This proved to be difficult to recruit since most orthopedic injuries occurred in the context of blast exposure. Finally, although our two TBI groups had a comparable proportion of single vs. multiple concussions, the sample size of our study is underpowered to properly evaluate this variable in the context of our behavioral and imaging data.

To conclude, we found common and distinct patterns of brain activation in blast-related and mechanical TBI. During correct inhibitions, both TBI groups demonstrated decreased activation in the DMN. In contrast, during failed inhibition trials, blast-related TBI exhibited hyperactivation and mechanical TBI produced hypoactivation. These divergent brain activation patterns were independent of self-reported complaints, including PTSD. The identification of an imaging test that is specifically sensitive to blast-related TBI in humans raises numerous clinical possibilities. It is conceivable that our brain activation patterns in response to an inhibitory control task could be used as a basis for the diagnosis of blast-related TBI in the clinical setting. The efficacy of potential treatments for the sequelae of blast-related TBI could also be measured with this imaging biomarker. This is critical since neuropsychological testing is relatively insensitive to the chronic effects of blast-related MTBI. Finally, these findings suggest

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

possibilities for developing an animal model for testing the effects of blast-related trauma on neural function based on inhibitory control testing.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Acknowledgements: This study was supported by grants from the U.S. Department of Defense (W81XWH-08-2-0124, W81XWH-10-1-0609).

Conflicts of Interest: No competing financial interests exist.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

References

1. Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C. and Castro, C.A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med 358, 453-463.
2. Hicks, R.R., Fertig, S.J., Desrocher, R.E., Koroshetz, W.J. and Pancrazio, J.J. (2010). Neurological effects of blast injury. J Trauma 68, 1257-1263.
3. Cernak, I. and Noble-Haeusslein, L.J. (2010). Traumatic brain injury: an overview of pathobiology with emphasis on military populations. J Cereb Blood Flow Metab 30, 255-266.
4. Risdall, J.E. and Menon, D.K. (2011). Traumatic brain injury. Philosophical Transactions of the Royal Society B-Biological Sciences 366, 241-250.
5. Terrio, H., Brenner, L.A., Ivins, B.J., Cho, J.M., Helmick, K., Schwab, K., Scally, K., Bretthauer, R. and Warden, D. (2009). Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. J Head Trauma Rehabil 24, 14-23.
6. Warden, D. (2006). Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil 21, 398-402.
7. Ling, G., Bandak, F., Armonda, R., Grant, G. and Ecklund, J. (2009). Explosive Blast Neurotrauma. Journal of Neurotrauma 26, 815-825.
8. Benzinger, T.L., Brody, D., Cardin, S., Curley, K.C., Mintun, M.A., Mun, S.K., Wong, K.H. and Wrathall, J.R. (2009). Blast-related brain injury: imaging for clinical and research applications: report of the 2008 st. Louis workshop. J Neurotrauma 26, 2127-2144.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

9. Hammeke, T.A.G., T.A. (2003). Traumatic Brain Injury. In: *Neuropsychiatry*. Schiffer, R.B., Rao, S.M., & Fogel, B.S. (ed). Lippincott Williams Wilkins: Philadelphia, pps. 1149-1167.

10. DePalma, R.G., Burris, D.G., Champion, H.R. and Hodgson, M.J. (2005). Blast injuries. N Engl J Med 352, 1335-1342.

11. Schneiderman, A.I., Braver, E.R. and Kang, H.K. (2008). Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. Am J Epidemiol 167, 1446-1452.

12. Garman, R.H., Jenkins, L.W., Switzer, R.C., 3rd, Bauman, R.A., Tong, L.C., Swauger, P.V., Parks, S.A., Ritzel, D.V., Dixon, C.E., Clark, R.S., Bayir, H., Kagan, V., Jackson, E.K. and Kochanek, P.M. (2011). Blast exposure in rats with body shielding is characterized primarily by diffuse axonal injury. J Neurotrauma 28, 947-959.

13. Saljo, A., Arrhen, F., Bolouri, H., Mayorga, M. and Hamberger, A. (2008). Neuropathology and pressure in the pig brain resulting from low-impulse noise exposure. J Neurotrauma 25, 1397-1406.

14. Saljo, A., Svensson, B., Mayorga, M., Hamberger, A. and Bolouri, H. (2009). Low-level blasts raise intracranial pressure and impair cognitive function in rats. J Neurotrauma 26, 1345-1352.

15. Goldstein, L.E., Fisher, A.M., Tagge, C.A., Zhang, X.L., Velisek, L., Sullivan, J.A., Upreti, C., Kracht, J.M., Ericsson, M., Wojnarowicz, M.W., Goletiani, C.J., Maglakelidze, G.M., Casey, N., Moncaster, J.A., Minaeva, O., Moir, R.D.,

Nowinski, C.J., Stern, R.A., Cantu, R.C., Geiling, J., Blusztajn, J.K., Wolozin, B.L., Ikezu, T., Stein, T.D., Budson, A.E., Kowall, N.W., Chargin, D., Sharon, A., Saman, S., Hall, G.F., Moss, W.C., Cleveland, R.O., Tanzi, R.E., Stanton, P.K. and McKee, A.C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med 4, 134ra160.

16. Bauman, R.A., Ling, G., Tong, L., Januszkiewicz, A., Agoston, D., Delanerolle, N., Kim, Y., Ritzel, D., Bell, R., Ecklund, J., Armonda, R., Bandak, F. and Parks, S. (2009). An introductory characterization of a combat-casualty-care relevant swine model of closed head injury resulting from exposure to explosive blast. J Neurotrauma 26, 841-860.

17. Wang, Y., Wei, Y., Oguntayo, S., Wilkins, W., Arun, P., Valiyaveettil, M., Song, J., Long, J.B. and Nambiar, M.P. (2011). Tightly coupled repetitive blast-induced traumatic brain injury: development and characterization in mice. J Neurotrauma 28, 2171-2183.

18. Risling, M., Plantman, S., Angeria, M., Rostami, E., Bellander, B.M., Kirkegaard, M., Arborelius, U. and Davidsson, J. (2011). Mechanisms of blast induced brain injuries, experimental studies in rats. Neuroimage 54 Suppl 1, S89-97.

19. Levin, H.S., Wilde, E., Troyanskaya, M., Petersen, N.J., Scheibel, R., Newsome, M., Radaideh, M., Wu, T., Yallampalli, R., Chu, Z. and Li, X. (2010). Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. J Neurotrauma 27, 683-694.

20. Belanger, H.G., Proctor-Weber, Z., Kretzmer, T., Kim, M., French, L.M. and Vanderploeg, R.D. (2011). Symptom complaints following reports of blast versus non-blast mild TBI: does mechanism of injury matter? Clin Neuropsychol 25, 702-715.

21. Slobounov, S.M., Gay, M., Zhang, K., Johnson, B., Pennell, D., Sebastianelli, W., Horovitz, S. and Hallett, M. (2011). Alteration of brain functional network at rest and in response to YMCA physical stress test in concussed athletes: RsFMRI study. Neuroimage 55, 1716-1727.

22. Zhang, K., Johnson, B., Gay, M., Horovitz, S.G., Hallett, M., Sebastianelli, W. and Slobounov, S. (2012). Default Mode Network in Concussed Individuals in Response to the YMCA Physical Stress Test. Journal of Neurotrauma 29, 756-765.

23. Scheibel, R.S., Newsome, M.R., Troyanskaya, M., Lin, X., Steinberg, J.L., Radaideh, M. and Levin, H.S. (2012). Altered brain activation in military personnel with one or more traumatic brain injuries following blast. J Int Neuropsychol Soc 18, 89-100.

24. Aron, A.R., Robbins, T.W. and Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. Trends in Cognitive Sciences 8, 170-177.

25. Dimoska-Di Marco, A., McDonald, S., Kelly, M., Tate, R. and Johnstone, S. (2011). A meta-analysis of response inhibition and Stroop interference control deficits in adults with traumatic brain injury (TBI). J Clin Exp Neuropsychol 33, 471-485.

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

26. Dockree, P.M. and Robertson, I.H. (2011). Electrophysiological markers of cognitive deficits in traumatic brain injury: a review. Int J Psychophysiol 82, 53-60.

27. Matthews, S., Simmons, A. and Strigo, I. (2011). The effects of loss versus alteration of consciousness on inhibition-related brain activity among individuals with a history of blast-related concussion. Psychiatry Res 191, 76-79.

28. Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R. and Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 88, 791-804.

29. Skinner, H.A. (1982). The Drug-Abuse Screening-Test. Addictive Behaviors 7, 363-371.

30. Spitzer, R., WIlliams JBW, GIbbon M, First, MB (1990). Structured Clinical Interview for DSM-III-R, Patient Edition/Non-Patient Edition (SCID-P/SCID-NP). American Psychiatric Press, Inc.: Washington, D.C.

31. Green, P. (2005). Word Memory Test for Windows: User's manual and program. Green's Publishing: Edmonton.

32. Cicerone, K.D. and Kalmar, K. (1995). Persistent Postconcussion Syndrome - the Structure of Subjective Complaints after Mild Traumatic Brain Injury. Journal of Head Trauma Rehabilitation 10, 1-17.

33. Weathers, F.W., Litz, B.T., Herman, D.S., Huska, J.A., Keane, T.M. (1993). The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. In: *9th Annual Conference of the ISTSS*: San Antonio.

34. Radloff, L.S. (1977). The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1.

35. Smith, A. (1968). The Symbol Digit Modalities test: A neuropsychologic test for learning and other cerebral disorders. Journal of Learning Disorders 3, 83-91.

36. (1944). Army Individual Test of General Ability. Manual of Directions and Scoring. War Department, Adjutant General's Office: Washington, D.C.

37. Lezak, M.D. (ed) 1995. Neuropsychological Assessment. Oxford University Press: Oxford

38. Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A. (2000). California Verbal Learning Test: Second Edition. Psychological Corporation: San Antonio.

39. Aron, A.R. and Poldrack, R.A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26, 2424-2433.

40. Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research 29, 162-173.

41. Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B. and Dale, A.M. (2004). Automatically parcellating the human cerebral cortex. Cerebral Cortex 14, 11-22.

42. Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S. and Killiany, R.J. (2006). An automated labeling system for subdividing the human cerebral

cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968-980.

43. Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. and Shulman, G.L. (2001). A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America 98, 676-682.

44. Binder, J.R. and Desai, R.H. (2011). The neurobiology of semantic memory. Trends in Cognitive Sciences 15, 527-536.

45. Zhang, S. and Li, C.S. (2012). Functional networks for cognitive control in a stop signal task: independent component analysis. Hum Brain Mapp 33, 89-104.

46. Kuo, J.R., Kaloupek, D.G. and Woodward, S.H. (2012). Amygdala Volume in Combat-Exposed Veterans With and Without Posttraumatic Stress Disorder A Cross-sectional Study. Archives of General Psychiatry 69, 1080-1086.

47. Sripada, R.K., King, A.P., Garfinkel, S.N., Wang, X., Sripada, C.S., Welsh, R.C. and Liberzon, I. (2012). Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci 37, 241-249.

48. Simmons, A.N. and Matthews, S.C. (2012). Neural circuitry of PTSD with or without mild traumatic brain injury: A meta-analysis. Neuropharmacology 62, 598-606.

49. McAllister, T.W. (2011). Neurobiological consequences of traumatic brain injury. Dialogues Clin Neurosci 13, 287-300.

50. Brunetti, M., Sepede, G., Mingoia, G., Catani, C., Ferretti, A., Merla, A., Del Gratta, C., Romani, G.L. and Babiloni, C. (2010). Elevated Response of Human

Amygdala to Neutral Stimuli in Mild Post Traumatic Stress Disorder: Neural Correlates of Generalized Emotional Response. Neuroscience 168, 670-679.

51. Liberzon, I., Taylor, S.F., Amdur, R., Jung, T.D., Chamberlain, K.R., Minoshima, S., Koeppe, R.A. and Fig, L.M. (1999). Brain activation in PTSD in response to trauma-related stimuli. Biological Psychiatry 45, 817-826.

52. Packard, M.G. and Knowlton, B.J. (2002). Learning and memory functions of the basal ganglia. Annual Review of Neuroscience 25, 563-593.

53. Stoodley, C.J. and Schmahmann, J.D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 46, 831-844.

54. O'Connor, D.A., Rossiter, S., Yucel, M., Lubman, D.I. and Hester, R. (2012). Successful inhibitory control over an immediate reward is associated with attentional disengagement in visual processing areas. Neuroimage 62, 1841-1847.

55. Minamoto, T., Osaka, M. and Osaka, N. (2010). Individual differences in working memory capacity and distractor processing: Possible contribution of top-down inhibitory control. Brain Research 1335, 63-73.

56. Belanger, H.G., Curtiss, G., Demery, J.A., Lebowitz, B.K. and Vanderploeg, R.D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. J Int Neuropsychol Soc 11, 215-227.

57. Vasterling, J.J., Brailey, K., Proctor, S.P., Kane, R., Heeren, T. and Franz, M. (2012). Neuropsychological outcomes of mild traumatic brain injury, post-

traumatic stress disorder and depression in Iraq-deployed US Army soldiers. British Journal of Psychiatry 201, 186-192.

58. Swick, D., Honzel, N., Larsen, J., Ashley, V. and Justus, T. (2012). Impaired Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury. Journal of the International Neuropsychological Society 18, 917-926.

59. Davenport, N.D., Lim, K.O., Armstrong, M.T. and Sponheim, S.R. (2012). Diffuse and spatially variable white matter disruptions are associated with blast-related mild traumatic brain injury. Neuroimage 59, 2017-2024.

60. Sharp, D.J., Bonnelle, V., De Boissezon, X., Beckmann, C.F., James, S.G., Patel, M.C. and Mehta, M.A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc Natl Acad Sci U S A 107, 6106-6111.

61. Floden, D. and Stuss, D.T. (2006). Inhibitory control is slowed in patients with right superior medial frontal damage. Journal of Cognitive Neuroscience 18, 1843-1849.

62. Iverson, G.L., Lange, R.T. and Franzen, M.D. (2002). Effects of mild traumatic brain injury exaggeration and malingering with the Trail Making Test. The Clinical Neuropsychologist 16, 398-406.

63. Mayer, A.R., Mannell, M.V., Ling, J., Gasparovic, C. and Yeo, R.A. (2011). Functional Connectivity in Mild Traumatic Brain Injury. Human Brain Mapping 32, 1825-1835.

Figure Legends

Figure 1. Schematic timeline for the Stop Signal Task (see Methods for details).

Figure 2. fROIs (shown in color) demonstrating significant main or interaction effects for the CI – GO, II – GO, and CI - II subtractions. Numbers correspond with brain region described in Table 3 and Figure 3. CI = correct inhibition, II = incorrect inhibition, GO = go conditions. Background gray-scale brain images derived from a rendering of the gray-white matter surface using Caret software (Washington University, St. Louis).

Figure 3. Bar graphs illustrating significant main and interaction effects for the CI – GO, II – GO, and CI - II subtractions. CI = correct inhibition, II = incorrect inhibition, GO = go trial conditions. Numbers in brackets correspond to brain regions shown in Figure 2 and described in Table 3. Note that regions 1-5 are from the CI – GO subtraction, regions 6-11 from the II – GO subtraction, and regions 12-13 are from the CI - II subtraction. Error bars = s.e.m.

Supplementary Figure 1. fROIs derived from the CI – GO (N=25), II – GO (N=39), and CI - II (N=24) subtractions. CI = correct inhibition, II = incorrect inhibition, GO = go trial conditions. Colors are used to demarcate distinct fROIs and have no interpretive significance. Background gray-scale brain images derived from a rendering of the gray-white matter surface using Caret software (Washington University, St. Louis).

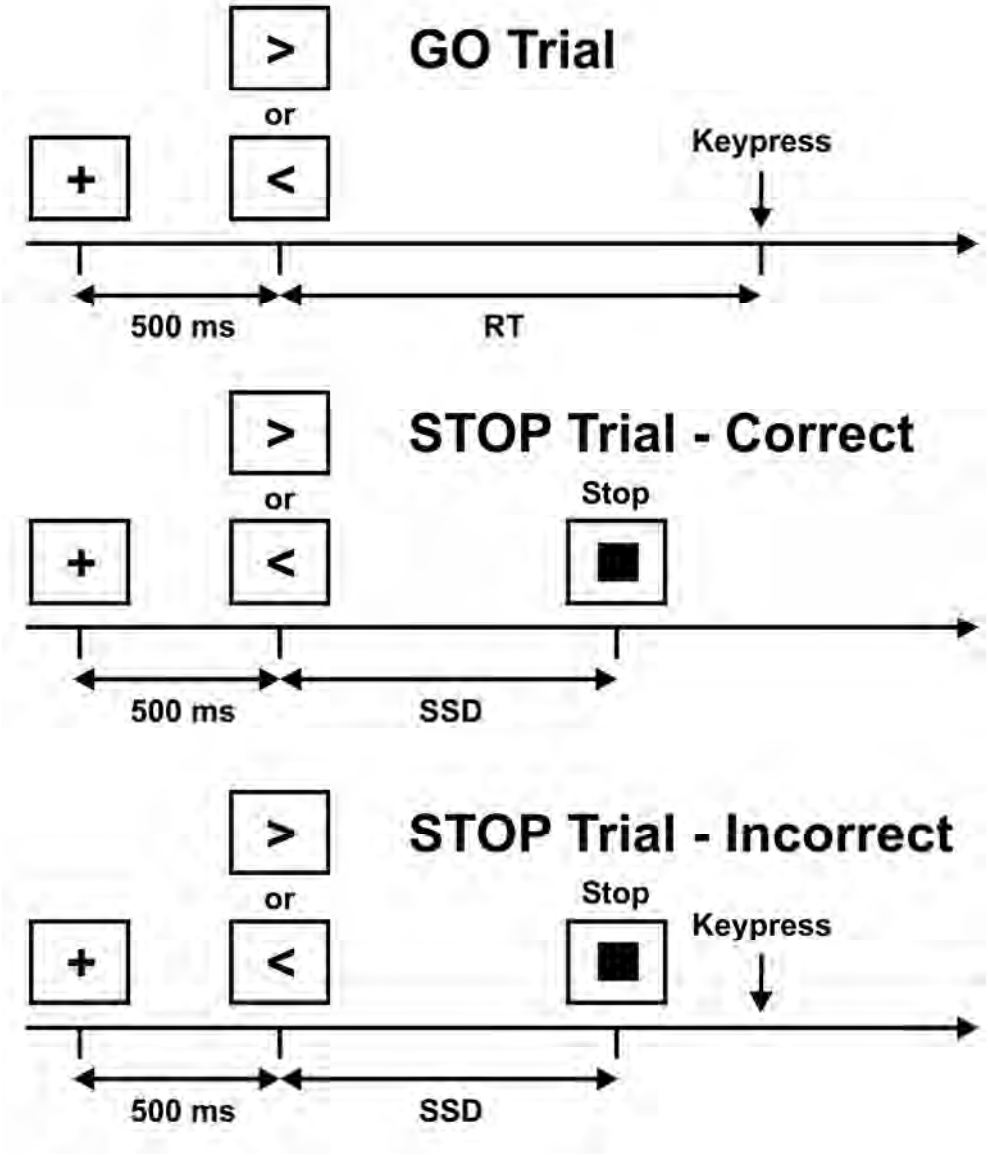


Figure 1
148x173mm (600 x 600 DPI)

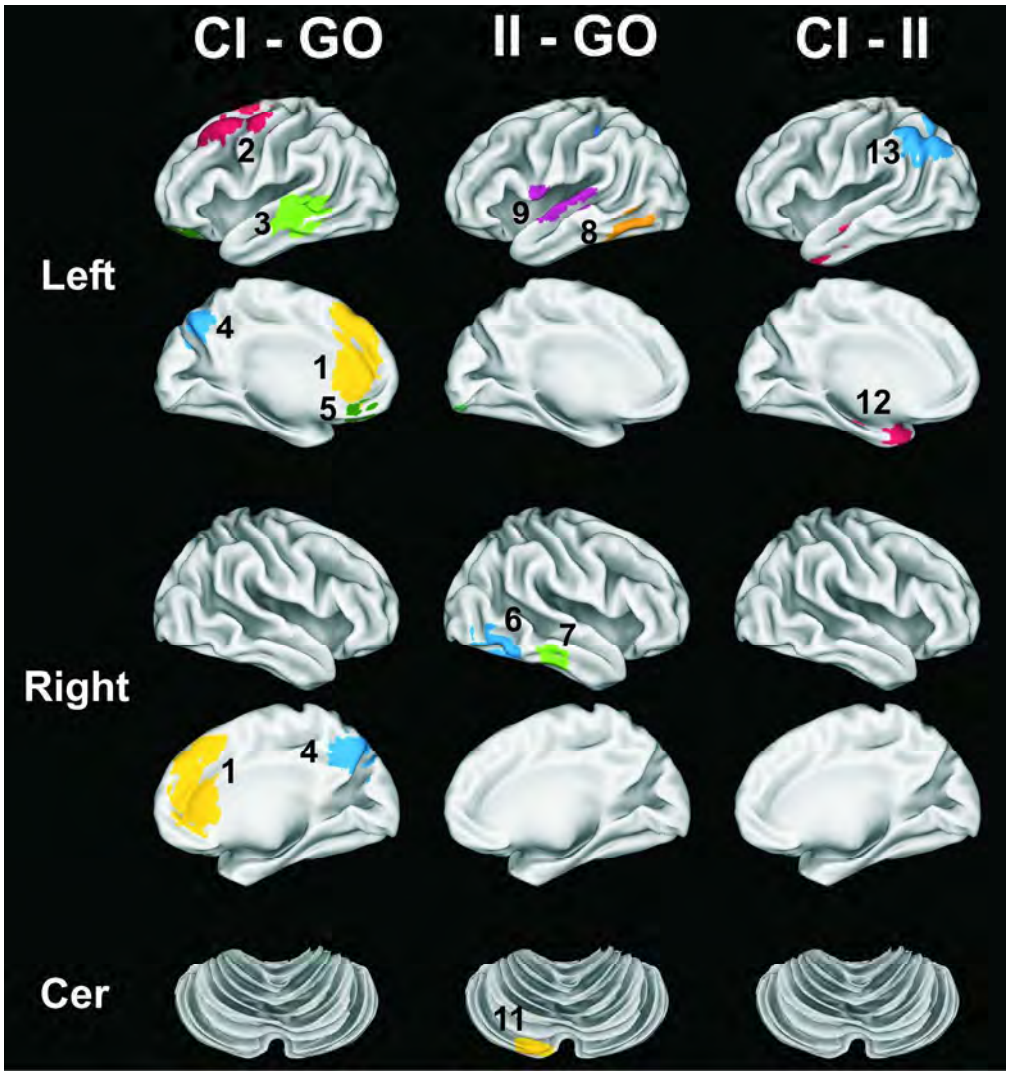


Figure 2
236x252mm (300 x 300 DPI)

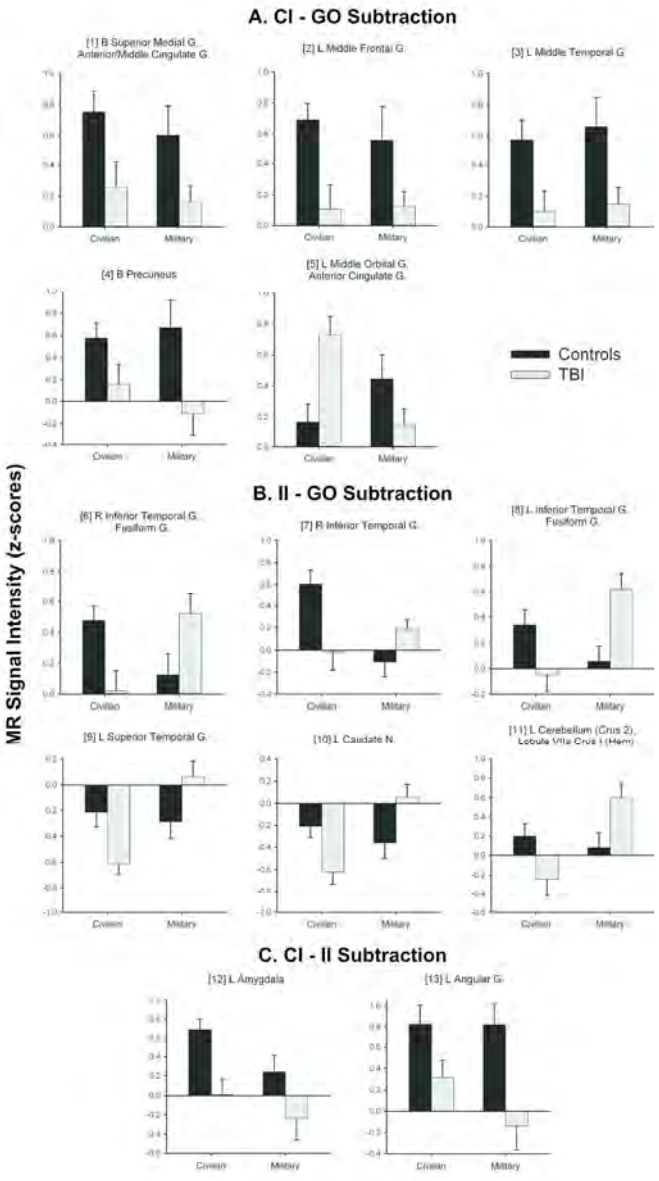
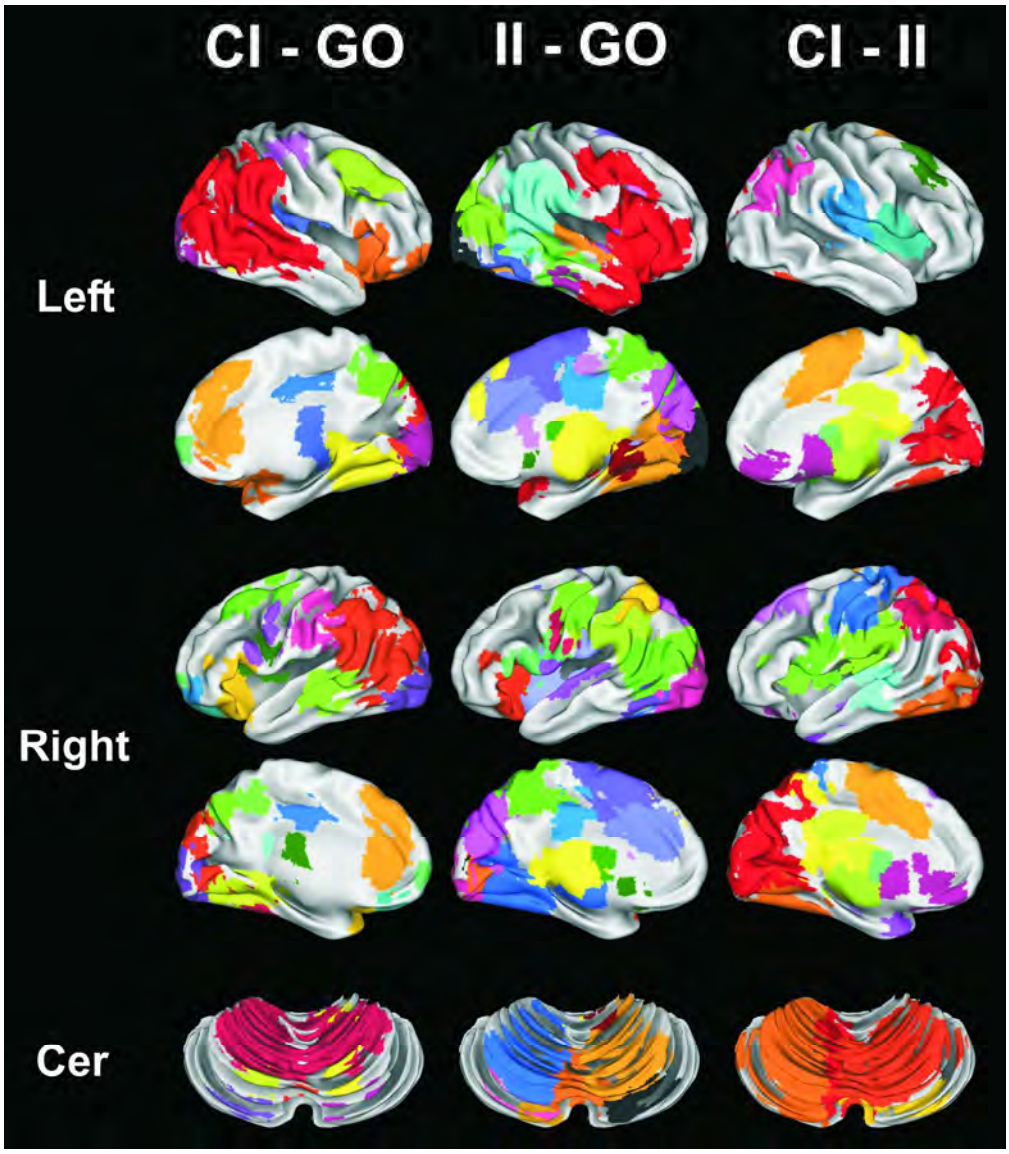


Figure 3
214x379mm (600 x 600 DPI)



Supplementary Figure 1
238x272mm (300 x 300 DPI)

Table 1. Demographic Information, TBI Injury Data, and Self-Report Ratings

Variable	milTBI (n = 21)	milCON (n = 22)	civTBI (n = 21)	civCON (n = 23)	2 X 2 ANOVA		
					TBI vs. CON	Mil vs. Civ	Interaction
Age - yrs	28.3 (4.6)*	29.7 (5.6)	26.2 (4.8)	27.3 (4.5)	-	0.033 (mil>civ)	-
Education - yrs	12.7 (1.3)	14.1 (2.2)	15.1 (1.8)	15.5 (2.4)	0.040(TBI<CON)	<0.001(mil<civ)	-
Sex - number (%) female	1 (4.7)	1 (4.5)	2 (9.5)	0 (0)	-	-	-
Handedness - number (%) right	18 (86)	22 (100)	20 (95)	20 (87)	-	-	-
Months since last TBI	52.9 (17.9)	NA	29.7 (16.1)	NA	-	-	-
Number (%) with >1 primary blast	16 (76.2)	NA	NA	NA	-	-	-
PCLC - total	53.8 (15.6)	24.9 (10.3)	24.7 (5.4)	25.0 (10.6)	<0.001(TBI>CON	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)
CESD - total	22.0 (12.1)	7.4 (9.3)	7.3 (7)	7.5 (7.2)	<0.001(TBI>CON	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)
Pain - total	3.1 (2.5)	0.6 (1.3)	0.9 (1.5)	0.6 (1.4)	<0.001(TBI>CON	0.007 (mil>civ)	0.003 (milTBI > milCON, civTBI, civCON)
Fatigue - total	4.1 (2.9)	2.2 (2.4)	2.4 (2.0)	2.8 (2.2)	-	-	-
NSI - total	33.1 (12.7)	7.9 (9.6)	10.5 (7.8)	8.4 (8.8)	<0.001(TBI>CON	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)

* Mean (SD), - = not significant.
TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, PCLC = PTSD Checklist - Civilian Version, CESD = Center for the Epidemiological Study of Depression Scale, NSI = Neurobehavioral Symptom Inventory.

Table 2. Neuropsychological Testing and Stop Signal Task Performance

					2 x 2 ANOVA		
Variable	**milTBI**	**milCON**	**civTBI**	**civCON**	**TBI vs CON**	**Mil vs Civ**	**Interaction**
Neuropsychological Testing							
Trails A - sec	26.5 (10.5)*	23.9 (4.6)	22.0 (7.2)	23.0 (9.7)	-	-	-
Trails B - sec	65.5 (41.1)	60.6 (26.8)	50.6 (20.0)	59.0 (28.9)	-	-	-
Trails B-A - sec	39.0 (34.2)	36.6 (24.5)	28.5 (19.1)	35.9 (25.4)	-	-	-
COWAT - total	36.9 (9.5)	36.9 (9.0)	43.6 (9.8)	43.6 (15.0)	-	0.007** (Mil < Civ)	-
CVLT Short Delay - total	9.6 (3.4)	10.2 (3.1)	11.6 (1.7)	10.7 (2.2)	-	0.030 (Mil < Civ)	-
CVLT Long Delay - total	9.4 (3.9)	10.8 (3.1)	12.0 (1.7)	10.6 (2.3)	-	-	0.041***
CVLT - T-score	50.4 (7.9)	49.6 (8.9)	52.2 (7.7)	52.5 (6.4)	-	-	-
SDMT - total written correct	51.5 (12.5)	58.2 (8.7)	61.8 (15.1)	61.2 (9.6)	-	0.010 (Mil < Civ)	-
SDMT - total oral correct	61.2 (13.7)	66.0 (11.1)	68.8 (16.3)	71.9 (12.1)	-	0.024 (Mil < Civ)	-
Stop Signal Task							
GO Correct - % correct	88.8 (7.3)	91.9 (6.3)	87.8 (8.7)	90.0 (6.7)	-	-	-
GO Correct - median RT (ms)	650.4 (84.7)	683.5 (77.7)	715.9 (64.9)	706.6 (94.2)	-	0.014(Mil < Civ)	-
STOP Correct - % correct	37.1 (4.8)	37.5 (4.8)	37.9 (4.6)	38.3 (4.6)	-	-	-
SSD - ms	499.8 (124.9)	545.3 (103.3)	596.0 (93.2)	607.9 (91.6)	-	0.0006 (Mil < Civ)	-
SSRT - ms	150.6 (85.3)	138.0 (59.4)	119.6 (58.2)	98.5 (77.9)	-	0.023 (Mil > Civ)	-

* Mean (SD), ** p-value, *** milTBI < civTBI (pairwise posthoc analysis), - = not significant.

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, SDMT = Symbol Digit Modalities Test, SSD = Stop Signal Duration, SSRT = Stop Signal Reaction Time

Table 3. Significant Functional ROIs from 2 (Mil / Civ) x 2 (TBI / CON) ANOVA

#		Region	BA	x	y	z	Vol. (ml)	2 X 2 ANOVA TBI vs. CON	Mil vs. Civ	Interaction
CI - GO Subtraction										
1	B	Superior Medial G., Anterior/Middle Cingulate G.	8, 9, 32	0.5	34.8	27.8	10.22	*	-	-
2	L	Middle Frontal G.	6,8	-35.2	10.4	50.2	2.49	*	-	-
3	L	Middle Temporal G.	21	-57.7	-31.6	-2.9	2.81	*	-	-
4	B	Precuneus	7	6.7	-64.0	37.9	2.74	*	-	-
5	L	Middle Orbital G., Anterior Cingulate G.	11	-15.2	41.3	-9.3	1.22	-	-	*
II - GO Subtraction										
6	R	Inferior Temporal G., Fusiform G.	37	48.9	-57.1	-15.2	2.07	-	-	*
7	R	Inferior Temporal G.	20	58.4	-26.0	-18.7	0.52	-	-	*
8	L	Inferior Temporal G., Fusiform G.	37	-50.8	-59.3	-16.3	1.10	-	-	*
9	L	Superior Temporal G.	22	-57.6	-12.9	3.5	1.00	-	-	*
10	L	Caudate N.	-	-21.7	-15.0	29.1	1.72	-	-	*
11	L	Cerebellum (Crus 2), Lobule VIIa Crus I (Hem)	-	-11.9	-83.9	-22.5	0.16	-	-	*
CI - II Subtraction										
12	L	Amygdala	-	-30.2	0.1	-21.3	1.89	*	-	-
13	L	Angular G.	39, 40	-43.3	-58.2	40.7	4.77	*	-	-

* Significant main or interaction effect, - = not significant.
TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, R = right, L = left, B = bilateral, G. = gyrus.

Supplementary Table 1. Correct Inhibitions - GO

Side	Region	BA	x	y	z	Vol. (ml)
Positive ROIs						
R	Angular G., Inf. ParietalL., Mid. Temporal & Occip. G.	7, 19, 21, 22, 37, 39, 40	47.3	-52.2	18.8	38.43
L	Mid. Occipital G., Mid. Temporal G., Angular G.	7, 19, 37, 39	-37.5	-62.2	23.6	22.71
R	Insula L., Inf. Frontal G. (p. Orbitalis)	44, 45	33.0	24.4	-4.7	12.30
B	Sup. Medial G., Ant. Cingulate C.	8, 9, 32	0.5	34.8	27.8	10.22
L	Insula L., Inf. Frontal G. (p. Orbitalis)	44, 45	-34.3	19.5	-2.5	8.91
R	Lingual, Fusiform G.	19, 37	22.3	-51.0	-6.0	5.24
L	Lingual, Fusiform G.	19, 37	-19.9	-54.8	-6.0	3.88
R	Mid. Frontal G.	6, 8	38.9	14.3	41.5	3.76
L	Mid. Temporal G.	21	-57.7	-31.6	-2.9	2.81
R	Precuneus	7	6.7	-64.0	37.9	2.74
L	Mid. Frontal G.	6, 8	-35.2	10.4	50.2	2.49
L	Precuneus	5	-3.0	-47.5	44.1	1.32
L	Sup. Medial G., Mid. Orbital G.	10	-4.1	60.3	6.4	1.26
L	Mid. Orbital G.	11	-15.2	41.3	-9.3	1.22
L	Mid. Orbital G.	11	-37.7	50.1	-1.0	0.84
B	Mid. Cingulate C.	23	-0.4	-18.4	36.7	0.82
Negative ROIs						
L	Inf. & Mid. Occipital, Calcarine G.	17, 18	-19.9	-87.1	-4.1	12.00
R	Inf. & Mid. Occipital, Calcarine G.	17, 18	20.2	-86.9	-0.7	8.62
B	Cerebellar Vermis (4/5)	-	-1.4	-50.2	-17.7	7.43
L	Putamen	-	-23.2	-10.7	15.7	7.09
R	Thalamus	-	22.8	-13.6	14.3	5.57
L	SupraMarginal G., Postcentral G.	1, 2, 3, 40	-46.8	-24.6	31.8	2.74
R	Postcentral G., Precentral G.	4	34.9	-24.0	50.8	1.57
L	Tapetum	-	-20.4	-43.8	25.1	1.35
L	Precentral G.	6	-56.0	2.6	27.4	1.18

Supplementary Table 2. Incorrect Inhibitions - GO

Side	Region	BA	x	y	z	Vol. (ml)
Positive ROIs						
R	Right Inf. Frontal G, Insula, Precentral G, Temporal Pole	6, 13, 38, 44, 45	43.2	12.4	6.9	36.99
L	Cuneus, Precuneus, Sup. Parietal Lobule	7, 17, 18, 19	-4.4	-71.7	29.5	21.99
R	Supramarg. G., Angular G., Sup. & Mid. Temporal G.	37, 39, 40	53.7	-44.2	19.3	17.57
L	Lingual G., Fusiform G., Calcalrine	19,37	-17.0	-51.3	-5.1	16.81
R	Lingual G., Fusiform G., Calcalrine	19,37	18.5	-57.5	-1.8	14.95
B	Ant. & Mid. Cingulate G.	24, 32	0.7	20.8	33.7	14.46
B	SMA	6	1.2	2.8	56.8	13.73
L	Insula Lobe, Inf. Frontal G.	13, 44, 45	-35.3	17.2	4.3	12.72
R	Thalamus	-	3.2	-20.7	5.8	10.46
B	Cerebellar Vermis (6)	-	0.0	-72.8	-3.9	10.06
L	SupraMarginal G. IPC	40	-53.0	-41.0	27.2	8.83
L	Precuneus	5, 7	-2.4	-47.9	51.8	7.31
R	Mid. & Sup. Occipital G.	19	37.4	-71.6	15.7	6.39
L	Mid. Occipital G.	19, 39	-31.5	-76.8	16.5	6.07
L	Mid. Temporal G.	19, 39	-48.1	-58.0	6.5	6.07
R	Mid. Temporal G.	21	51.7	-28.8	-5.7	4.16
L	Rolandic Operculum, Precentral G.	44	-52.0	4.5	12.3	3.05
L	Postcentral, Precentral G.	4, 6	-42.3	-13.5	42.8	2.44
L	Inf. Parietal Lobule	7	-35.6	-50.4	42.1	2.42
L	Insula L.	13	-40.0	-9.7	5.1	2.19
R	Inf. Temporal, Fusiform G.	37	48.9	-57.1	-15.2	2.07
L	Caudate N.	-	-12.0	2.6	11.1	1.72
B	Mid. Cingulate C.	23, 31	0.2	-21.0	35.9	1.70
L	Inf. Temporal G., Inf. Occip. G.	19	-50.8	-59.3	-16.3	1.10
R	ParaHippocampal G.	-	19.3	-40.4	-3.3	1.07
R	Caudate N.	-	12.2	2.5	13.0	0.89
R	Inf. Temporal G.	20	58.4	-26.0	-18.7	0.52
R	Sup. Parietal L.	7	22.8	-61.3	40.4	0.46
B	Sup. Medial G.	9	4.3	41.7	40.1	0.39
L	Precentral G.	4, 6	-49.0	-8.7	25.4	0.28
L	Cerebellum (Crus 2), Lobule VIIa Crus I (Hem)	-	-11.9	-83.9	-22.5	0.16

Negative ROIs

L	Inf. & Mid. Occipital, Calcarine G.	17, 18	-22.3	-85.9	-3.6	12.98
R	Inf. & Mid. Occipital, Calcarine G.	17, 18	22.9	-86.9	-2.1	11.79
R	Caudate N.	-	19.7	5.7	23.3	4.68
L	Caudate N.	-	-21.7	-15.0	29.1	1.72
R	Sup. Temporal G.	22	57.5	-11.1	6.1	1.15
L	Sup. Temporal G.	22	-57.6	-12.9	3.5	1.00
R	Hippocampus	-	28.3	-37.0	8.7	0.81
L	Caudate N.	-	-12.3	19.9	0.9	0.78

Supplementary Table 3. Incorrect Inhibitions - Correct Inhibitions

Side	Region	BA	x	y	z	Vol. (ml)
Positive ROIs						
L	Cuneus, Precuneus, Calcarine, Lingual G.	7,17,18	-6.2	-68.6	13.0	45.19
B	SMA	6	0.6	-0.2	49.8	11.74
L	Cerebellum (VI)	-	-29.9	-57.8	-17.3	10.89
L	Thalamus	-	-8.3	-23.2	15.1	9.26
R	Thalamus	-	10.2	-18.8	12.4	8.73
L	SupraMarginal G.	40	-48.8	-26.4	21.3	7.48
R	Cerebellum (VI)	-	18.3	-58.8	-14.9	6.12
L	Postcentral G.	3	-36.1	-22.5	46.4	5.62
R	Insula Lobe	13	40.4	6.8	10.7	4.89
R	Rolandic Operculum, Supramarginal G.	40,13	46.0	-22.8	19.1	4.78
L	Thalamus	-	0.8	-22.2	-3.8	3.97
L	Rolandic Operculum	13	-46.0	-1.4	15.4	3.06
L	Insula Lobe	13	-33.5	16.7	12.1	2.17
L	Pallidum	-	-12.4	-0.1	7.7	1.70
R	Pallidum	-	16.0	0.3	6.7	1.42
R	Cerebellum (VIII)	-	15.8	-73.3	-30.3	1.13
L	Sup. Parietal Lobule	5, 7	-19.4	-44.5	60.3	0.50
Negative ROIs						
B	Caudate, Ant. Cing., Orbital, Rectal G	11, 12, 25, 32	-0.1	25.8	-3.0	6.22
L	Angular G., Inf. Par.	39, 40	-43.3	-58.2	40.7	4.77
R	Angular G., Inf. Par.	39, 40	44.5	-60.8	37.4	4.03
L	Sup., Mid. Frontal G.	8	-23.1	22.3	49.9	3.35
L	Mid. Temporal G.	21	-60.0	-28.7	-2.2	2.15
L	Amygdala	-	-30.2	0.1	-21.3	1.89
R	Mid. Frontal G.	8	29.1	22.5	47.8	1.25